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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/710,058	11/10/2000	David Anderson	A-68531-1/RMS/JJD/SPL	4112

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EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/710,058	ANDERSON ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,16 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,16 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendment dated 4/2/04 is hereby acknowledged.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 1-3, 16, and 20 are currently pending and under consideration (to the extent of the elected invention.).

Election/Restriction

2. Applicant's election without traverse of Group I (claims 1-9) and the species rGFP in Seq. Id. 1 in Paper No. 10 is again acknowledged.

Withdrawn Objection (s) and/or Rejection (s)

Applicants amendment and arguments relating thereto have overcome the following rejection:

The rejection of claims 2, 3, 16 and 20 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (lack of written description).

Outstanding Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 103

3. Claims 1-3 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bryan et al. US Pat. No. 6,232,107 (5/01: filed 10/98 or earlier)with attached Result 4 DATABASE Alignment search and Aran et al. Cancer Gene Therapy, Vol. 5, No. 4 pages 195-206 (1998). .

Bryan et al. disclose and claim the use (e.g. diagnostics and "high throughput screening" e.g. libraries) of nucleic acid molecules encoding green fluorescent proteins (e.g. bioluminscent) from the genus Renilla, including reference Seq. ID No. 15 which is 98.4% (with best local similarity of 99.4%) homologous to elected seq. ID 1, differing by only one nucleotide (C vs. G) and reference Seq. Id. No. 16 which has 100% sequence identity to the presently claimed Renilla GFP of Seq. Id. 2. See e.g. Reference Seq. Id 15 and attached Result 4 DATABASE Alignment search; and Reference sequence Id. 16. . Bryan et al. teach the use of the bioluminescent green fluorescent proteins in cellular assays (e.g. live cells, including mammalian) and in high throughput screening systems (e.g. employing libraries) (e.g. see col. 2-3; 14). The reference further teaches the use of a "fusion partner" (e.g. a targeting agent as "a first gene") in its genetic fusion constructs. See e.g. col. 24. . Although teaching green fluorescent proteins from other sources, the use of renilla green fluorescent proteins is "more ideal for use as an analytical tool" (e.g. see col. 4-5); see also patent claims directed to Renilla sequence Id 15 and 16.

The Bryan et al. reference differs from the presently claimed invention (e.g. see claim 1) in failing to explicitly teach the use of a retrovirus as a vector;

and the use of "human codon optimized nucleic acid encoding a Renilla GFP"(see claim 20).

However, the Bryan et al. reference clearly teaches vectors:

a. "the [S]election and use of such vehicles" as being "well within the skill of the artisan"; and

b. in mammalian hosts including "recombinant *virus*" , as well as plasmid and phages. See e.g. col. 23 (especially bottom) to col. 24.

But, the Aran et al. reference teaches the favorable use of retroviral vectors, both in vitro and in vivo including an internal ribosome entry site (IRES) for fusion constructs preferably comprising "optimized, humanized" (e.g. see page 204, left column for benefits of humanizing) GFP (e.g. *Aequorea victoria*) ; since "[T]his vector allows rapid and specific identification of the expressed protein (e.g. MDR1 gene transfer) in living cells (e.g. mammalian cells) ..." (E.g. see Abstract and page 195, especially right column).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize a retroviral vector as the "recombinant virus" vector and a humanized GFP disclosed for use in the Bryan et al. reference in order to appreciate the benefits thereof ; e.g. rapid and specific identification of the expressed protein.

4. Claims 1-3, 16 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aran et al. Cancer Gene Therapy, Vol. 5, No. 4 pages 195-206 (1998)

and Bryan et al. US Pat. No. 6,232,107 (5/01: filed 10/98 or earlier)with attached Result 4 DATABASE Alignment search.

Aran et al. (e.g. see abstract and entire article) disclose and teach retroviral vectors which "comprise" an "optimized , humanized" (compare to present claim 20) GFP gene (e.g. a red-shifted green fluorescent protein from *Aequorea victoria*) and which further include a "first gene" (e.g. for multridrug resistance: MDR) and an internal ribosome entry site (e.g. IRES) which is expressed in living cells (e.g. "A cell" ie. mammalian as presently claimed); along with Beta galactosidase.

Although teaching the use of an *Aequorea victoria* GFP gene sequence in its vector/fusion constructs/libraries, the Aran et al. Reference differs from the presently claimed invention (e.g. claims 14-19) by failing to explicitly teach the use of a *Renilla* GFP gene sequence which encodes a GFP that is at least 90%, 95%, 100% identical to SEQ Id. 2.

However, Bryan et al. disclose and claim the use (e.g. diagnostics and "high throughput screening" e.g. libraries) of nucleic acid molecules encoding green fluorescent proteins (e.g. bioluminscent) from the genus Renilla, including reference Seq. ID No. 15 which is 98.4% (with best local similarity of 99.4%) homologous to elected seq. ID 1, differing by only one nucleotide (C vs. G) and reference Seq. Id. No. 16 **which has 100% sequence identity to the presently claimed Renilla GFP of Seq. Id. 2.** See e.g. Reference Seq. Id 15 and attached Result 4 DATABASE Alignment search; and Reference sequence Id. 16. . Bryan et al. teach the use of the bioluminescent green fluorescent proteins in cellular

assays (e.g. live cells, including mammalian) and in high throughput screening systems (e.g. employing libraries) (e.g. see col. 2-3; 14). The Bryan reference further teaches the use of a "fusion partner" (e.g. a targeting agent) in its genetic fusion constructs. See e.g. col. 24. **Although teaching green fluorescent proteins from other sources e.g. *Aequorea victoria;*, the use of renilla green fluorescent proteins is "more ideal for use as an analytical tool" (e.g. see col. 4-5); see also patent claims directed to Renilla sequence Id 15 and 16.**

Thus, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize the Bryan et al. polynucleotide Renilla green fluorescent protein (including seq. Id 15) in the Aran et al. genetic constructs for purposes of performing screening assays (e.g. high throughput library screens) in order to obtain the benefits of the renilla protein in such assays as taught by the Bryan reference.

5. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over the obviousness rejections using Aran et al. And Bryan et al. as applied to claims 1-3, 16 and 20 above, and, if necessary, further in view of Zolutukhin et al. US Pat. No. 5,874,304 (2/99: filed 1/96).

The above combined teaching of the Aran et al. and Bryan et al. References as described in the above obviousness rejections is hereby incorporated by reference in their entirety.

The reference differ from the presently claimed invention (e.g. claim 20) by failing to *explicitly* teach a human codon-optimized nucleic acid encoding a Renilla GFP (e.g. humanized GFP) in a retroviral vector.

However, Zolutukhin et al. teach that utilizing human codon-optimized nucleic acid GFP in nucleic acid constructs (including fusion proteins; e.g. col. 4 corresponding to present claim 2 "first gene" terminology) included in vectors (e.g. see col. 5, examples; particularly retroviral: see patent claims, especially claims 50 and 69) contained in cells (e.g. see patent claims 71-80) in which the constructs contain:

1. GFP (particularly Renilla: see col. 1 , last paragraph; col. 14 and Table 1; and especially col. 16, lines 3-15: "... spectrum of Renilla ... preferable to that of Aequorea);

2. IRES elements (e.g. see col. 13; particularly patent claims 50 and 62) serves to overcome prior art obstacles and is advantageous (e.g. improved expression in mammalian and human cells) (e.g. see col. 1-2).

Accordingly, one of ordinary skill in the art at the time of applicant's invention would have been motivated to utilize "human codon-optimized nucleic acids expressing Renilla GFP in the genetic constructs (e.g. cells/vectors comprising renilla GFP/IRES elements) rendered obvious by the combined Aran et al. And Bryan et al. teaching in light of the advantages thereof imparted by such humanized sequences as taught by the Zolutukhin et al. reference.

Thus, it would have been prima facie obvious to one of ordinary skill at the time of applicant's invention to modify the cellular/vector genetic constructs

taught by the Aran and Bryant reference to include human codon-optimized (e.g. humanized) nucleotides encoding renilla GFP in order to obtain the advantages thereof as taught by the Zolutukhin et al. reference.

6. Claims 1-3, 16 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zolutukhin et al. US Pat. No. 5,874,304 (2/99: filed 1/96) and Bryan et al. US Pat. No. 6,232,107 (5/01: filed 10/98 or earlier)with attached Result 4 DATABASE Alignment search.

The Zolutukhin et al. reference teaches that utilizing human codon-optimized nucleic acid GFP in nucleic acid constructs (including fusion proteins; e.g. col. 4 corresponding to present claim 2 "first gene" terminology) included in vectors (e.g. see col. 5, examples; particularly retroviral: see patent claims, especially claims 50 and 69) contained in cells (e.g. see patent claims 71-80) in which the constructs contain:

1. GFP (particularly Renilla: see col. 1 , last paragraph; col. 14 and Table 1; and especially col. 16, lines 3-15: "... spectrum of Renilla ... preferable to that of Aequorea);

2. IRES elements (e.g. see col. 13; particularly patent claims 50 and 62) serves to overcome prior art obstacles and is advantageous (e.g. improved expression in mammalian and human cells) (e.g. see col. 1-2).

Although the Zolutukhin et al. reference teaches nucleic acid which employ the preferential use of Renilla GFP the Zolutukhin reference differs from the presently claimed invention by failing to explicitly teach the use of a *Renilla*

GFP gene sequence which encodes a GFP that is at least 90%, 95%, 100% identical to SEQ Id. 2.

Bryan et al. disclose and claim the use (e.g. diagnostics and "high throughput screening" e.g. libraries) of nucleic acid molecules encoding green fluorescent proteins (e.g. bioluminscent) from the genus Renilla, including reference Seq. ID No. 15 which is 98.4% (with best local similarity of 99.4%) homologous to elected seq. ID 1, differing by only one nucleotide (C vs. G) and reference Seq. Id. No. 16 **which has 100% sequence identity to the presently claimed Renilla GFP of Seq. Id. 2.** See e.g. Reference Seq. Id 15 and attached Result 4 DATABASE Alignment search; and Reference sequence Id. 16. . Bryan et al. teach the use of the bioluminescent green fluorescent proteins in cellular assays (e.g. live cells, including mammalian) and in high throughput screening systems (e.g. employing libraries) (e.g. see col. 2-3; 14). The Bryan reference further teaches the use of a "fusion partner" (e.g. a targeting agent) in its genetic fusion constructs. See e.g. col. 24. **Although teaching green fluorescent proteins from other sources e.g. *Aequorea victoria;*, the use of renilla green fluorescent proteins is "more ideal for use as an analytical tool" (e.g. see col. 4-5); see also patent claims directed to Renilla sequence Id 15 and 16.**

Thus, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize the Bryan et al. polynucleotide Renilla green fluorescent protein (including seq. Id 15) in the Zolutukhin reference. genetic constructs since:

a. Zolutukin teaches the preferential use of Renilla GFP thus motivating the selection of the functionally equivalent Bryan Renilla GFP obvious to one of ordinary skill in the art; and/or

b. one of ordinary skill in the art would have been motivated to select the Bryan reference Renilla sequences for r purposes of performing screening assays (e.g. high throughput library screens) in order to obtain the benefits of the renilla protein in such assays as taught by the Bryan reference.

Discussion

Applicant's arguments directed to the above obviousness rejections over the Aran et al. , Bryan et al. and Zolutukhin reference references were considered but deemed nonpersuasive for the following reasons.

Regarding the Aran reference applicant argues that "Aran's teachings (e.g. regarding retroviral vector constructs) are not generic for any GFP" but are restricted to *Aequorea victoria* since the reference examples (referring to page 196, col. 1, first full paragraph) specifically address a "humanized, red-shifted green fluorescent protein (GFP) from the jelly fish *Aequorea victoria* and wild-type GFP" (wtGFP).

Applicant's arguments that the Aran et al. reference teaching is strictly limited to its example of vectors/cells comprising *Aequorea* GFP fails to consider the Aran reference teaching as a whole which represents a generic teaching of the use of GFP's in general. For example, both the title and the abstract reference to GFP generically. E.g. "We have also incorporated the improved features of GFP as a reporter gene..." and the article nowhere limits its

exemplified retroviral genetic construct, and the benefits thereof, as being specific only to *Aequoria* GFP . It is noted that the above rejections referr to the Aran et al. teaching of *Aequoria* GFP as being exemplary of GFP's in general [" GFP gene (e.g. a red-shifted green fluorescent protein from *Aequorea victoria*) "]

.

Further, in response to applicant's arguments against the Aran reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this regard, as pointed out in the above rejections, the Bryan reference teaches the interchange ability of the *Renilla* and *Aequoria* GFP's in vector constructs. Applicant is also directed to the above rejection citing "**Although teaching green fluorescent proteins from other sources e.g. *Aequorea victoria;*, the use of renilla green fluorescent proteins is "more ideal for use as an analytical tool" (e.g. see col. 4-5)"; and also patent claims directed to *Renilla* sequence Id 15 and 16.**

Applicant further argues that *"Aequorea* and *Renilla* GFP's are **not** interchangeable (and indeed the result of their substitutability is unpredictable) in a retroviral vector" citing Aran first full paragraph of page 204: "when a retroviral vector encoding a wild type *Aequorea* vector was introduced into a mammalian cell fluorescence was *undetectable"; in* contrast with encoding a wild type

Renilla GFP (as disclosed in the Examples of instant application) which produces detectable levels of GFP in mammalian cells.

Applicant's argument was considered but deemed nonpersuasive for the following reasons.

Initially, applicant fails to consider the Aran reference teaching as a whole and is additionally misguided as to its analysis of the Aran teaching. In this respect applicant focuses on the Aran reference teaching with respect to the wild type (wt) GFP while completely ignoring the more relevant Aran teaching regarding the modified GFP (e.g. optimized, humanized red-shifted GFP) and the improved Aran retroviral construct which is more relevant regarding the presently claimed invention. In this respect Aran (in the same paragraph alluded to by applicant but not addressed) further teaches that optimized, humanized, red shifted GRP displayed MUCH MORE green fluorescence than "wtGFP"; with the additional benefit of the retroviral system being nontoxicity to the cells, which represented a previously reported problem. Additionally, it is noteworthy that the next three paragraphs further extrapolate the benefits of using a modified (as compared to the wtGFP) in the retroviral system for GFP expression over other reporter gene systems. Accordingly, applicant's argument is not persuasive since it focuses on (wt)GFP while ignoring the benefits of utilizing the more germaine teaching regarding optimized humanized GFP and additionally fails to acknowledge the reference's teaching of the benefits of utilizing the modified GFP in the reference's retroviral expression system.

Applicant further argues that *Aequorea* GFP and *Renilla* GFP share on the order of only about 25% amino acid sequence identity which renders their corresponding expression in a mammalian cell utilizing a retroviral vector unpredictable (e.g. no reasonable expectation of success). This argument was considered but deemed nonpersuasive for the following reasons.

First, by focusing on wild-type, applicant is failing to address the Aran and Bryan modified sequences which are @t 100% identical. Accordingly, applicant's focus on wild-type Renilla sequences when modified sequences are at issue moots applicant's arguments with regard to the above rejection. Additionally, applicant fails to address the combined teaching of the Aran and Bryan references, especially when such teachings are interpreted as a whole to one of ordinary skill in the art.

Applicant argues that "at the time of filing of the instant application, there was no way of knowing if Renilla GFP could be successfully expressed in a mammalian cell using a retroviral vector citing the following references in support:

1. Hanazono Hum. Gene Ther. Vol 8:1313-9 (1997): "many attempts by our laboratory to isolate stable retroviral producer cell clones secreting biologically active vectors containing either the highly fluorescent S65T-GFP mutant or humanized GFP have *failed*" [Exhibit A];

2. Levy et al. Nature Biotech. Vol. 14:610-14 (1996) ("...wildtype could never be visualized by fluorescence microscopy (table 1)" [Exhibit B]; and

3. Cheng et al. Nature Biotech. Vol. 14:606-609 (1996)("the expression and detection of wildtype GFP in mammalian cells reportedly *failed*"[Exhibit C]. Additionally, with regard to the Zolutukhin reference (cited for providing human codon optimized GFP) applicant argues that "given the unpredictability in the field with respect to expression of a GFP from a retroviral vector, providing a human codon-optimized GFP does nothing to cure this problem in the art" citing the Hanazono reference teaching in support. According to applicant: "Until the work was actually done, there was no reasonable expectation of success of producing Renilla GFP in a mammalian cell using a retroviral vector". Applicant's arguments directed to the above-recited references were considered but deemed nonpersuasive for the following reasons.

Applicant has failed to properly consider the whole teaching of the references cited in the above rejection (especially Aran et al.) in conjunction with applicant's cited prior art.

The Hanazono reference (e.g. see abstract) was unable to isolate stable retroviral producer cell clones secreting biologically active vectors containing *either* the highly fluorescent S65T-GFP mutant **OR** humanized GFP due to gene rearrangement or other mutations that abrogated GFP expression resulting in the author's conclusion that "GFP may not be an appropriate reporter gene for gene transfer applications **in our vector/packaging systems**". (emphasis provided: see Abstract).

Importantly, the Levy and Cheng reference (Exhibits B and C) cited above are specifically addressed by the Aran et al. reference on page 204, left column.

As pointed out by applicant above, the Levy and Cheng references, consistent with the Aran reference, were unable to obtain good fluorescence **with wildtype GFP** utilizing a retroviral vectors in mammalian cell types. However Aran et al. further points out that: "Cheng et al. and Levy et al. have recently shown efficient expression of a humanized, red-shifted GFP when introduced through retroviral vectors into different cell types" (see Aran et al. Page 204, left column 1st four sentences). Accordingly, the Cheng and Levy reference (as well as Aran) teach toward the use of modified GFP (in contrast to wild-type GFP) in retroviral vectors to promote cell expression.

However, in this respect Aran et al. further states: "Our vector, similar to their (e.g. Cheng/Levy) vectors, included an **improved version of GFP**. The two new features of this *second-generation GFP* are a S65T gain of function mutant, which results in a red-shifted excitation peak with increased brightness, **and** the conversion of jellyfish GFP codons to human codon usage, which results in higher expression levels because of a more efficient translation in mammalian cells. **Using the humanized, red-shifted GFP, a single copy of the integrated viral genome has been shown to be sufficient for production of detectable fluorescence.** " (emphasis provided).

Accordingly, the use by Aran et al of *a second-generation GFP* mutant which incorporates BOTH S65T-GFP mutant **AND** humanized GFP represented an improvement over the prior art (e.g. Hanazono, Levy and Cheng).

Additionally, the Aran et al. reference further taught an improved vector/packaging systems (over that taught of Hanazono, Levy and Cheng) since

the Aran et al. "retroviral system is NONTOXIC to the cells, as has been previously reported (referring to footnotes 34,35 which corresponds to the Cheng and Levy references cited as exhibits B and C above). See Aran et al. Page 204, left column bottom of 1st full paragraph.

The Aran et al. reference further points to improvements in its vector construct (e.g. linking the starting codon of GFP to the 3' end of the IRES sequence; and the use of the MDR phenotype) which results in further optimization leading to the usefulness of its construct *in vivo* and in *gene therapy* applications. See Aran Abstract; pages 204-205.

In short, the Aran et al. reference represents a vector (e.g. retroviral) packaging system employing *a second-generation GFP* which possesses more than a reasonable expectation of being expressed in mammalian cell(s) as taught by Aran.

Applicant further argues that Bryan "does nothing to overcome the unpredictability in the field with respect to expression of a GFP in a retroviral vector". Additionally, Applicant argues that "Bryan only describes transient transfection and expression of a Renilla GFP in a mammalian cell using a vector that is not a retroviral vector" and therefore Aran et al and Bryan are not combinable. These arguments were considered but deemed nonpersuasive for the following reasons.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce

the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As pointed out in the rejections above, there is ample motivation to combine the Aran and Bryant references including:

a. The equivalency of utilizing GFP from different sources as taught by Bryant: e.g. other sources of GFP (including *Aequorea*) can be used, *renilla* green fluorescent proteins is "more ideal for use as an analytical tool"; and/or

b. the Bryan et al. reference clearly teaching vectors:

-. "the [S]election and use of such vehicles" as being "well within the skill of the artisan"; and

-. **in mammalian hosts** including "recombinant ***virus***" , as well as plasmid and phages. See e.g. col. 23 (especially bottom) to col. 24 which suggest the use of retroviral vector systems and mammalian host cells such as that disclosed in the Aran reference.

Additionally, in response to applicant's arguments against the Bryan reference (or Aran reference) individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further, as discussed above, the Aran et al. reference provides more than a reasonable expectation that use of a second generation GFP (from *Renilla* or *Aequorea*) in the Aran et al. retroviral packaging system would by favorably expressed in a mammalian cell (s).

Thus, for all the reasons recited above, the obviousness rejections are hereby maintained.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Future Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
June 7, 2004